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ORIGINAL CONTRIBUTIONS

Vasectomy and Prostate Cancer in US Blacks and Whites

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A large population-based case-control study was carried out to investigate the association between vasectomy and prostate cancer risk in black and in white men in the United States. Study subjects resided in the geographic areas covered by the population-based cancer registries of the Georgia Center for Cancer Statistics, or the Metropolitan Detroit Cancer Surveillance System, or in 10 counties included in the cancer registry of the New Jersey State Health Department. Cases for this study were men aged 40–79 years identified from pathology and outpatient records at hospitals covered by these registries, newly diagnosed with pathologically confirmed prostate cancer between August 1, 1986, and April 30, 1989. Population controls less than age 65 years were selected at periodic intervals by random digit dialing. Older controls were systematically selected (after a random start) from computerized records of the Health Care Finance Administration. A statistically nonsignificant excess risk (odds ratio (OR) = 1.6, 95% confidence interval (CI) 0.5–4.8) for prostate cancer associated with vasectomy was noted in blacks. Overall, the risk for prostate cancer associated with vasectomy in whites was not elevated (OR = 1.1, 95% CI 0.8–1.7). An increase in risk was found, however, for white men who had had a vasectomy 20 years or more prior to study (OR = 1.7, 95% CI 0.9–3.3) or who had had a vasectomy at less than age 35 years (OR = 2.2, 95% CI 1.0–4.4). For the total study group, the odds ratio associated with men who had a vasectomy 20 or more years prior to study was 1.5 (95% CI 0.8–2.7), and the odds ratio associated with men who had had a vasectomy at less than age 35 years was 2.0 (95% CI 1.0–4.0). Further detailed analysis showed that young age at vasectomy (less than age 35 years) was a more important risk factor than was years since vasectomy. *Am J Epidemiol* 1993;137:263–9.

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Abbreviations: CI, confidence interval; OR, odds ratio.

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Prostate cancer is a major disease whose causal factors are only partially understood. On the basis of US age-adjusted rates for 1985–1989, prostate cancer is the most common form of cancer in US black men (incidence, 140 per 100,000; mortality, 50 per 100,000) and a leading cause of cancer among US white men (incidence, 99 per 100,000; mortality, 23 per 100,000). Over 11 percent of US men will develop this disease in their lifetime (1). Recent studies have drawn attention to the possibility that vasectomy may increase the risk of developing prostate cancer (2–10). About 500,000 vasectomies are performed annually in the United States alone (11).

If vasectomy increases prostate cancer occurrence, the impact could be substantial. We have carried out a large study, which included similar numbers of black and of white prostate cancer cases and population-based controls, to examine the reasons for the large racial difference in risk for this disease. The study included data on history of vasectomy and related factors.

MATERIALS AND METHODS

This case-control study of prostate cancer was one component of a multicenter study of cancers of the esophagus, pancreas, prostate, and multiple myeloma in US blacks and whites. Pacific Islanders, Asians, American Indians, and Alaskan natives were excluded. Study subjects resided in the geographic areas covered by the population-based cancer registries of the Georgia Center for Cancer Statistics, or the Metropolitan Detroit Cancer Surveillance System, or in the 10 counties included in the cancer registry of the New Jersey State Health Department.

Cases for this study were men aged 40–79 years identified from pathology and outpatient records at hospitals covered by these registries, newly diagnosed with pathologically confirmed prostate cancer between August 1, 1986, and April 30, 1989. To ensure a broad distribution by race and age, we selected varying proportions of cases for inclusion in the study from among the total number of cases identified in each age-race group. The planned sampling frequency ranged from 100 percent for those younger than age 55 years to 20 percent for white males aged 65–74 years and 17 percent for black males aged 65–74 years.

Population controls were selected in the three geographic areas proportional to the expected age, sex, and race distribution of the combined cases for the four cancer sites. Population controls less than age 65 years were selected at periodic intervals by random digit dialing (12). Older controls were systematically selected (after a random start) from computerized records of the Health Care Finance Administration stratified by age (65–69, 70–74, and 75–79 years), sex, and race (black or white), for each geographic area. In-person interviews were conducted with the cases and controls, usually in the subject's home. Prostate cancer cases and male controls were interviewed concerning demographics, dietary intake, tobacco use, occupational history, sexual activity, and family history of cancer. A number of questions were asked regarding medical history, including history of prostate surgery and vasectomy. Regarding vasectomy, subjects were asked: "Have you had a vasectomy, that is, a sterilization operation for men?" Those responding yes were asked: "How old were you when you had your vasectomy?" Medical records of the cases were abstracted for diagnostic confirmation of prostate cancer.

Odds ratios for prostate cancer were calculated by logistic regression analysis (13). The odds ratios were adjusted for age (40–49, 50–54, . . ., 70–74, ≥75 years) and race (black or white), and when indicated, for other factors.

RESULTS

A total of 1,292 cases and 1,767 controls were identified for study. Interviews were obtained for 988 (76 percent) cases and 1,336 (76 percent) controls. After adjustment for nonresponse in the initial phase of screening for eligibility among random digit

dialing contacts, the response rate in controls was 70 percent. Six cases and six controls were dropped from the study because of incomplete interviews, and 16 subjects (15 controls and one case) were excluded because of a prior history of prostate cancer. Analyses for the association of prostate cancer risk with vasectomy excluded subjects who failed to report on vasectomy status (three cases and 15 controls) and subjects who reported a vasectomy within 5 years of interview (13 cases and eight controls). The subjects for analysis comprise 965 cases (471 blacks and 494 whites) and 1,292 controls (589 blacks and 703 whites) (table 1). In the study group, 56 cases (5.8 percent) and 83 controls (6.4 percent) reported a history of vasectomy 5 or more years prior to study.

As shown for study controls in table 2, history of vasectomy was strongly associated with age, race, and education. Among subjects with 0–8 years of schooling, only one subject (0.3 percent) reported a vasectomy. Vasectomy was also infrequent among the more elderly of the controls. A total of 75 (11 percent) white and eight (1 percent) black controls reported having had a vasectomy, with the prevalence reaching a maximum level of 19 percent in whites aged 40–59 years with 12 or more years education. A logistic regression main effects model (table 3) showed strong independent effects of age, race, and education on vasectomy prevalence.

For prostate cancer cases, the prevalence of vasectomy was examined by tumor grade.

TABLE 1. Prostate cancer cases and population-based controls by age and race, Atlanta, Georgia, Detroit, Michigan, and New Jersey, 1986–1989

Age (years)	Race				Totals	
	Black		White			
	Cases	Controls	Cases	Controls	Cases	Controls
40–59	121	225	158	312	279	537
50–69	182	181	156	214	338	395
≥70	168	183	180	177	348	360
Total	471	589	494	703	965	1,292

TABLE 2. Prevalence of vasectomy by age, race, and education in population-based controls, Atlanta, Georgia, Detroit, Michigan, and New Jersey, 1986–1989

Age (years) at study	Years of education*						Total	
	0–8		9–11		≥12		Black	White
	Black	White	Black	White	Black	White		
40–59								
No. of subjects	36	20	56	32	133	258	225	310
No. of vasectomies	0	0	4	5	3	49	7	54
%	0	0	7	16	2	19	3	17
60–69								
No. of subjects	67	23	44	32	70	158	181	213
No. of vasectomies	0	1	1	5	0	10	1	16
%	0	4	2	16	0	6	1	8
≥70								
No. of subjects	111	44	32	30	40	100	183	174
No. of vasectomies	0	0	0	1	0	4	0	5
%	0	0	0	3	0	4	0	3
Total								
No. of subjects	214	87	132	94	243	516	589	697
No. of vasectomies	0	1	5	11	3	63	8	75
%	0	1	4	12	1	12	1	11

* Education was unknown for six subjects, none of whom had had vasectomies.

The prevalence of vasectomy was about 6 percent for cases with grade 1 as well as for those with more advanced tumors.

As shown in table 4, for blacks the age-adjusted odds ratio for prostate cancer associated with vasectomy was 1.6 (95 percent confidence interval (CI) 0.5–4.8). The risk was unchanged by further adjustment for education. The relations between years since vasectomy and age at vasectomy were difficult to examine in blacks because the frequency of vasectomy was so low.

For whites, the age-adjusted odds ratio for prostate cancer was 1.1 (95 percent CI 0.8–1.7). The risk, compared with that for subjects without a vasectomy, was increased for those reporting vasectomy 20 or more years prior to study (odds ratio (OR) = 1.7, 95 percent CI 0.9–3.3) and for subjects reporting a vasectomy at age 25–34 years (OR = 2.2, 95 percent CI 1.0–4.4). For whites and blacks combined, the age- and race-adjusted odds ratio for prostate cancer was 1.2 (95 percent CI 0.8–1.7). The risk, compared with subjects without a vasectomy, was increased for those reporting vasectomy 20 or more years prior to study (OR = 1.5, 95 percent CI 0.8–2.7) and for subjects reporting a vasectomy at age 25–34 years (OR = 2.0, 95 percent CI 1.0–4.0).

In table 5, the risk for prostate cancer is shown with respect both to years since vasectomy and to age at vasectomy. Excess risk is shown for vasectomy at a young age irrespective of the time period prior to study of the vasectomy procedure. No excess is shown for subjects who had a vasectomy at age 35 years or more. The risk for prostate cancer associated with vasectomy at less than age 35 years was unchanged by statistical adjustment for study site, education, income, cigarette use, fat intake, body mass, history of prostate surgery, and number of sexual partners.

TABLE 3. Logistic main effects model for vasectomy in controls, Atlanta, Georgia, Detroit, Michigan, and New Jersey, 1986–1989

Characteristic	Odds ratio	95% confidence interval
Age (years)		
≥70*	1.0	
60–69	2.6	0.9–7.1
40–59	6.9	2.7–17.7
Race		
Black*	1.0	
White	7.7	3.6–16.5
Education (years)		
0–8*	1.0	
9–11	14.6	1.9–113
≥12	9.7	1.3–71.8

* Reference category.

TABLE 4. Vasectomy and risk of prostate cancer by vasectomy status, Atlanta, Georgia, Detroit, Michigan, and New Jersey, 1986–1989

	Race						Total	
	Black			White				
	Cases/controls	Odds ratio*	95% confidence interval	Cases/controls	Odds ratio*	95% confidence interval	Odds ratio†	95% confidence interval
Vasectomy								
No	464/581	1.0		445/628	1.0		1.0	
Yes	7/8	1.6	0.5–4.8	49/75	1.1	0.8–1.7	1.2	0.8–1.7
Years since vasectomy								
5–9	3/4	2.2	0.4–12.6	6/11	0.9	0.3–2.6	1.2	0.5–2.9
10–19	1/1	1.4	0.1–23.4	23/46	0.9	0.5–1.6	1.0	0.6–1.6
≥20	3/3	1.2	0.2–6.4	20/18	1.7	0.9–3.3	1.5	0.8–2.7
Age (years) at vasectomy								
≥45	4/2	2.3	0.4–13.0	15/23	0.9	0.5–1.8	1.0	0.5–1.8
35–44	3/4	2.2	0.4–12.3	17/34	0.9	0.5–1.7	1.0	0.6–1.3
25–34	0/2			17/18	2.2	1.0–4.4	2.0	1.0–4.0

* Adjusted for age (40–49, 50–54, . . . , 70–74, ≥75 years).
† Adjusted for age (40–49, 50–54, . . . , 70–74, ≥75 years) and race.

TABLE 5. Vasectomy and risk of prostate cancer by years since and age at vasectomy, Atlanta, Georgia, Detroit, Michigan, and New Jersey, 1986–1989

Age (years) at vasectomy	Years since vasectomy					
	5–19			≥20		
	No. of cases	Odds ratio*	95% confidence interval	No. of cases	Odds ratio*	95% confidence interval
<35	6	2.2	0.8–6.5	11	1.8	0.7–4.6
≥35	27	0.9	0.6–1.5	12	1.2	0.6–2.8

* Adjusted for age (40–49, 50–54, . . . , 70–74, ≥75 years) and race.

DISCUSSION

In this large population-based case-control study, the prevalence of vasectomy was strongly associated with age, race, and education. The findings for vasectomy and prostate cancer risk in blacks are based on small numbers of exposed subjects, but are consistent with an increased risk. The low prevalence of vasectomy in blacks, however, indicates that this surgical treatment could not be related to the marked increased risk for prostate cancer in this group.

In whites and in the combined group of whites and blacks, vasectomy was associated with an excess risk for prostate cancer only among subjects who had undergone vasectomy at less than age 35 years. An association of risk with greater time since vasectomy was found, on further analysis, to be restricted to the group that had a vasectomy at less than age 35 years. Statistical adjustment for age, education, and a number of other possibly associated factors did not alter the main findings.

Vasectomy has been associated with an increased risk for prostate cancer in four studies (2–5). Honda et al. (2), in a Los Angeles study of 216 white ever-married cases aged 60 years or less and matched population-based controls, found a prevalence of vasectomy of 23 percent in the controls and an associated risk for prostate cancer of 1.4. The risk by year since vasectomy increased to 4.4 for subjects who had had a vasectomy 30 or more years prior to study. Rosenberg et al. (3) studied 220 prostate cancer cases and hospital-based controls, aged 40–69 years, from an ongoing multipurpose case-control surveillance study in several US east-coast cities. They found a prevalence of vasectomy in the controls of about 3 percent and an associated relative risk of 3.6 to 5.9. No tendency was noted for the risk to increase with time since vasectomy, up to 15 years or greater, or with age at vasectomy. Mettlin et al. (4) studied 614 prostate cancer cases aged 50 or more years and hospital-based controls at a New York cancer center. Subjects who reported a vasectomy within 5 years of diagnosis were excluded. They found a prevalence of vasectomy in the controls of 5 percent and an associated relative risk of 1.7. Risk increased with time since vasectomy to 2.2 for 13–18 years and 1.5 for 19 or more years. Giovannucci et al. (5) examined mortality rates in a retrospective cohort of husbands of members of the Nurse's Health Study. Data were obtained by questionnaire in 1989 on 14,607 men who had undergone vasectomy as of 1976 and 14,607 men who had not. The risk for prostate cancer mortality was 0.3-fold associated with less than 20 years since vasectomy and was 2.5-fold associated with 20 or more years since vasectomy. The findings were based upon only six cases and did not reach statistical significance.

Several other studies that examined vasectomy and prostate cancer risk have shown no association or weaker associations (6–10). Ross et al. (6) studied 110 prostate cancer cases and population controls, aged 80 years or less, from a California retirement community. No excess risk was found. Another small study by Newell et al. (7) of 110 white prostate cancer cases and hospital con-

trols at a Texas cancer center also found no association. Nienhuis et al. (8) identified one case of prostate cancer in a young cohort of 13,246 men with a vasectomy. Sidney (9) followed 5,332 vasectomized men with a mean age 46.6 years and 15,996 nonvasectomized men for prostate cancer who were enrolled from 1977–1982 and followed through 1984, for a mean follow-up of 4.6 years. The 17 cases of prostate cancer found in vasectomized men were not in excess compared with the rate in the nonvasectomized group. More recently, Sidney et al. (10) extended their follow-up to 6.8 years from baseline interview and again, with 135 cases studied, they found no association of vasectomy with prostate cancer risk. In further detailed analyses in this study, no associations were found either with years since vasectomy or age at vasectomy.

Our study involved a large number of prostate cancer cases, and special efforts were made to study both black and white men, with oversampling of men who developed prostate cancer at a relatively young age. The control group was population based. A limitation of this study is the reliance on self-reports of vasectomy. Vasectomy may be falsely reported by cases who have confused procedures related to the diagnosis and treatment of prostate cancer. For this reason, as in the study of Mettlin et al. (4), we excluded subjects from analysis who had reported vasectomy within 5 years of study. We do not know the extent of similarly biased reporting by cases for the periods prior to this time and, without medical record confirmation, cannot accurately assess its effects. The association we found of increased risk for prostate cancer with time since vasectomy is strikingly similar to that found by others (2, 4). On further detailed analysis, however, our data suggest a somewhat stronger relation of prostate cancer risk with age at vasectomy than with years since vasectomy, although these two temporal factors are difficult to clearly disentangle. Most of the negative studies were small (6–9) or, for the cohort studies, had short duration of follow-up. Only the recent study by Sidney et al. (10) provides evidence for a lack of association of prostate cancer with vasectomy 20 or more years prior to disease development.

Because the basis for human prostate carcinogenesis is only poorly understood, a specific role for vasectomy in the etiology of this disease can only be speculated upon. Major long-term changes in serum steroid hormone profiles probably do not occur after vasectomy (14), although more subtle alterations such as loss of seasonal variation in serum luteinizing hormone, estradiol, and testosterone (15) and abnormalities in serum gonadotropin response (16) have been reported for men several years after vasectomy. Men with vasectomy have a high prevalence of antibodies to spermatozoa (17) because of the disruption of the barrier system that normally sequesters germ cells and other reproductive products from the rest of the body. In a study of BDF_1 mice (18), vasectomy resulted in increased occurrence of tumors of the liver and lung in association with increased antisperm immunity. Ablin et al. (19) found increased antibodies to sperm in prostate cancer cases, as well as in cases of other genitourinary cancers and of benign prostatic hyperplasia, suggesting that their finding reflects a host response to aberrant genitourinary cellular alterations rather than a causative factor. Although vasectomy does not lead to gross changes in prostate morphology (20), reductions in seminal plasma volume and total ejaculate contents of zinc, magnesium, and citric acid in men 8 years after vasectomy have been reported. In addition, the polyamines, spermidine and spermine, but not their precursor, putrescine, were reduced (21). In addition, the androgens testosterone and dihydrotestosterone may be reduced in seminal plasma after vasectomy (22). The polyamines are major components of cellular membranes and may serve as markers of cell turnover. Studies of the effects of vasectomy on the endocrine and immunologic systems and on prostate physiology are generally limited in time of postvasectomy investigation. Long-term effects over several decades have not been studied, and the possible association with prostate carcinogenesis has been ex-

plored insufficiently. In addition, the specific influence on prostate pathology of age at vasectomy is unclear.

Our study provides support for the hypothesis that vasectomy is related to an increased risk for prostate cancer, indicating that the association may be restricted to men who have had a vasectomy at a young age. As the prevalence of vasectomy is low in blacks compared with whites, the large excess of prostate cancer in blacks cannot be attributed to this procedure.

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